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(54) Title: BIOLOGICALLY ACTIVE COMPOSITES AND METHODS FOR THEIR PRODUCTION AND USE

(57) Abstract: Biologically active composites containing calcium phosphate, more specifically beta-tri-calcium phosphate, and methods of preparing the same are disclosed herein. Also disclosed are methods of restoring an osseous void and complimentary kits for the disclosed composites.

BIOLOGICALLY ACTIVE COMPOSITES AND METHODS FOR THEIR PRODUCTION AND USE

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims benefit of U.S. provisional patent application Serial No. 60/242,906 filed October 24, 2000, the contents of which are hereby incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] This patent application relates to biologically active composites containing calcium phosphate and methods of preparing the same. Also included are methods of restoring an osseous void using the composites of the present invention and to kits for the preparation and delivery of such composites. In accordance with the invention, the composites can be prepared using calcium phosphate in a variety of different forms, including morsels and blocks. The composite mass generally contains osteoconductive properties and may also exhibit osteoinductive and osteogenic potential by nature of the β-TCP materials.

BACKGROUND OF THE INVENTION

[0003] When bone integrity is threatened by trauma, infection, congenital malformation, tumor growth or degenerative diseases, a method of regenerating and healing the affected bone is the use of bone grafts. Bone grafts function in a manner similar to cancellous bone – supporting new tissue growth by providing the bone and blood cells with a matrix through which to interweave, as they reconnect the bone fragments.

[0004] There are three processes that are characteristic of a successful bone graft.

(1) osteoconduction - the apposition of growing bone to the three-dimensional surface of a suitable scaffold provided by the graft;

(2) osteoinduction - the biologically mediated recruitment and differentiation of cell types essential for bone; and

(3) osteogenesis - the process of bone formation through cellular osteoblastic activity and remodeling through osteoclastic activity, which, in turn, is dependent upon the presence of osteoprogenitor stem cells.

[0005] Orthopedists in this field currently use a variety of materials when attempting to enhance these three processes. A sampling of these materials include the autograft, cadaveric allograft, xenograft, and several types of graft materials. These materials are considered basic types of bone substitutes that are used alone and sometimes in combination.

[0006] Autogenous bone is generally widely used in this field. Autogenous bone grafts, or autografts, have a number of advantages. They are histocompatible, they do not transfer disease and they retain viable cells that contribute to the formation of new bone

including osteoblasts. Histocompatibility, for example, allows the cellular reaction that accompanies implantation to proceed without an immunologic rejection of the graft, and the graft generally integrates well into the graft site. Autografts can be prepared from cancellous bone or cortical bone. However, the latter material typically lacks the porosity required for cellular migration and revascularization.

[0007] The anterior or posterior aspect of the iliac crest provides a common donor site from which to harvest autograft material. Donor material from the iliac crest provides osteogenic properties in the form of surviving osteogenic precursor cells. The loose trabecular structure of the iliac crest encourages ingrowth of blood vessels that are necessary to support bone growth by helping to reduce ischemic necrosis of cellular elements. The noncollagenous bone matrix proteins of the iliac crest include growth factors and also provide osteoinductive properties. The bone mineral and collagen in the autograft material transplanted from the iliac crest provide a compatible osteoconductive surface.

[0008] Unfortunately, the full potential of autografts are not fully realized in practice because graft processing results in the death of much of the cellular elements. Those cells that survive must initially receive their oxygen via diffusion. Thus, considerable anoxic cell death probably occurs before sufficient vascularization has permeated the graft. Revascularization into the internal regions of the autograft is slow and incomplete and can be inhibited by fibrin clotting in the autograft and by the packing procedure used to place the graft into the surgical site. Packing of the autograft into a surgical site can decrease the porosity of the graft, in turn decreasing the potential for revascularization of the innermost areas of the graft. Cell death in the autograft leaves behind only a bone mineral scaffold.

[0009] Among several other shortcomings, the harvesting process of autograft is high in cost. Other shortcomings include the limited quantity of bone available for harvest, significant donor-site morbidity (rates as high as 25%), temporary disruption of donor-site bone structure, complications such as infection and pain, increased operative time and significantly increased operative blood loss. Minor complications include superficial infection and seromas, and minor hematomas. More serious complications include herniation of abdominal contents through massive bone graft donor sites, vascular injuries, deep infections at the donor site, neurologic injuries, deep hematoma formation requiring surgical intervention and iliac wing fractures.

[0010] Autograft alternatives include allografts, xenografts and synthetic bone grafts. Allografts are bone grafts harvested from a human donor other than the recipient. They are usually cleaned and processed to remove cells and debris to minimize their potential for eliciting an immune response or to carry infectious agents. Such tissue can be preserved by processes that can compromise mechanical properties like freeze-drying or freezing. As a result of this processing, allografts do not contain living cells and are not osteogenic. Although their properties vary with preparation methods, they generally have osteoconductive properties and can exert a somewhat stimulatory (osteoinductive) effect on cell in-migration and differentiation.

[0011] Xenografts are harvested from animals. Because of their immunogenicity, xenografts harvested from another species have generally been impractical for clinical use. Removal of proteinaceous and fatty materials during processing, as is done in the preparation of Kiel bone, or Oswestry bone, reduces immunogenicity. However, the processing required to produce this type of graft removes the osteoinductive matrix

proteins. To guarantee viral inactivation, not only cells, but all proteins must be removed, thus eliminating both osteogenic and osteoinductive potential.

[0012] As a result, alternative bone-grafting strategies have been investigated. The development of composite grafts that combine synthetic cancellous bone void fillers with autogenous bone-forming cells could simplify and improve grafting procedures.

[0013] There have been devices in the art which allow for the mixing of bodily fluids within a syringe comprising inorganic particles and morsels. Few of these devices, however, provide a device that allows for the formation of a biologically active composite capable of fostering osteoinduction, osteogenesis, and osteoconduction.

[0014] For example, U.S. Patent No. 4,551,135 ("Gorman") discloses a syringe for the extrusion of a semi-plastic mass, having a barrel which may be pre-loaded with a semi-plastic mass or one component of a multi-component plasticizable mixture, and which may be fitted at its exit end with removable means for making an inter-connection with a filling syringe to a add a second liquid, component to the dispensing syringe. In a preferred embodiment, Gorman teaches that the barrel is flared toward its lower end.

[0015] U.S. Patent No. 4,065,360 ("Kreb") discloses a syringe device for drawing blood or other fluids directly into a sealed sterile environment. The syringe includes a hollow housing, a movable piston, at least one culture cavity in the walls of the housing and sealing means about the periphery of the movable piston such that after fluid is withdrawn into contact with the culture cavities, the piston may be moved back upwardly to seal the culturing media with respect to the outside environment and to the chamber within the syringe to allow for sterile culturing of the fluid. Kreb also teaches a hollow nipple means attached to one end of the syringe adapted to receive a needle.

[0016] U.S. Patent No. 4,801,263 ("Clark") discloses a device for placing osseous implant substances into interdental alveolar bone defects. The device includes a syringe barrel member having an inlet and an outlet, a syringe plunger member having a piston rod, grasping members attached to an external surface of the syringe barrel and a threaded nozzle coupler attached to the exterior of the barrel member for allowing an extended nozzle member, preferably curved, to be attached to the syringe barrel.

[0017] U.S. Patent No. 5,772,665 ("Glad") discloses a device for mixing a pharmaceutical composition which includes a hollow body having an outlet sealed by a removable closure, a plunger slidable therein in sealing contact with the inner wall of the hollow body, actuating means for displacing the plunger, a chamber for housing the pharmaceutical composition, a filling conduit connected to the chamber, and a check valve associated with the conduit and the chamber which prevents flow from the chamber but permits flow into the chamber through the conduit. Glad discloses that water can be added to the chamber in one of two ways: withdrawing the plunger upward and allowing water to enter through the lower end; or by placing the lid on the lower end, removing the plunger and pouring/injecting water into the upper opening. When the filling is complete, either the lid is applied to the lower end or the plunger is re-inserted into the hollow body, respectively.

[0018] U.S. Patent Nos. 5,824,084 and 6,049,026 (referred to herein collectively as "Muschler") disclose a method of preparing a composite bone graft and apparatus for preparing an implantable graft, respectively, which includes a porous, biocompatible, implantable substrate, a container for retaining the substrate and for permitting flow of a bone marrow aspirate suspension (bone marrow aspirate that may include an isotonic solution and an anti-coagulant) completely through the substrate into an effluent container

for receiving effluent of the bone marrow aspirate suspension from the container. Muschler also teaches a graft having an enriched population of connective tissue progenitor cells, the graft being the resultant product of the disclosed method and apparatus.

[0019] Accordingly, there is a need to provide methods of preparing a biologically active composite material that is osteoconductive, osteoinductive and osteogenic.

[0020] There is a need to provide biologically active composite materials that are made of porous inorganic material and an infiltrant.

[0021] There is a need to provide methods for restoring an osseous void for situations requiring the use of a bone void filler for filling voids or gaps.

[0022] There is a need to provide methods to fill spaces between two bony structures to allow fusion, such as between the vertebral bodies of the spine.

[0023] Moreover, there is a need in the art to provide a kit that can form a biologically active composite and deliver the composite mass into an osseous void thereby restoring the void.

SUMMARY OF THE INVENTION

[0024] This invention provides methods for preparing biologically active composite materials comprising aspirating or absorbing an infiltrant into at least one porous, biocompatible material; and maintaining the infiltrant and the porous material in contact under conditions effective to achieve at least partial coagulation of the infiltrant and porous material to form a self-supporting body. The porous, biocompatible material of the present invention can have pore volumes as low as 30%. Preferably, however, there exist other forms of this invention where the biocompatible material can have pore volumes of

at least 70%, 85%, 88% or 90% to allow for proper infiltration of therapeutic materials. The biocompatible material can comprise synthetic bone mineral, ceramic material, calcium phosphate material, tri-calcium phosphate material or beta-tri-calcium phosphate. The porous material can be resorbable and at least one porous, biocompatible material is comprised of a resorbable beta-tri-calcium phosphate with interconnected micro-, meso- and macro-pores that render said at least one porous, biocompatible material at least 90% porous. The porous material can have pores with diameters down to less than 10 μm up to about 100 μm or greater. The aspirating or absorbing step can comprise aspirating therapeutic material onto the porous material or drawing bone marrow into a body of a syringe at least partially containing the porous material. The maintaining step can take place within a syringe or molded body to form a self-supporting body. The methods of the invention can further comprise manipulating the self-supporting body. The method can be further augmented by adding a composition such as a medicament to the self-supporting body or to the porous material. The infiltrants used in the present invention can be a variety of therapeutic materials.

[0025] In another aspect, the present invention provides methods for restoring osseous voids. Such methods comprise placing in the void at least a portion of a self-supporting body comprising partially coagulated infiltrant or therapeutic material in admixture with a porous, biocompatible material. The portion may be shaped to fit the void. Placement can be effected using a syringe, a tube, an insertion guide, a catheter or a shaped mould. The infiltrant can be bone marrow aspirate, replicated bone marrow or any therapeutic material.

[0026] The present invention also provides methods for restoring intraosseous voids comprising the steps of preparing the void, providing an aspirating means for holding

porous, biocompatible material, aspirating bone marrow from an animal using the aspirating means or infiltrating the material with a therapeutic, so as to produce a biologically active composite of the aspirate/infiltrant and the porous material. The aspirate/infiltrant is allowed to at least partially coagulate, the composite is removed from the aspirating means and a portion of the composite is placed in the void. The aspirating means can be a syringe or other device capable of holding the composite and capable of acting as a delivery device. The composite can be shaped to fit said void prior to insertion into said void. The composite can be delivered into said void by syringe. The aspirate can be allowed to coagulate for a period of time and any remaining resultant composite can be preserved for later use. This preservation can be by freezing.

[0027] In yet another aspect, the present invention provides kits for the preparation and delivery of biologically active composites. In preferred embodiments, such kits comprise an instrument for the injection and the withdrawal of one or more fluids, as well as a porous, biocompatible material. The kits can also contain a plurality of syringes or pre-evacuated tubes. The biocompatible material can be in morsel or block form. The kits can also have a cutting instrument or spatula.

[0028] The present invention also provides an apparatus capable of housing a porous biocompatible material. The material is infiltrated with a biological substance to provide a biological composite. In one embodiment, the present invention provides an apparatus for preparing a biological composite comprising a material chamber, having a proximal end and a distal end, containing a calcium phosphate material having macro-, meso- and micro-porosity, the proximal end being sealingly closed by a movable plunger; and the distal end of the chamber being closed by a dismountable end cap, the end cap being provided with a point for attachment of an aspiration needle. In certain embodiments, the

apparatus further comprises a closed end cap that is interchangeable with the dismountable end cap for sealing the material chamber between the plunger and the closed end cap.

[0029] In another embodiment of the present invention, there is provided a method for preparing a biological composite comprising the steps of: providing an apparatus comprising a material chamber comprising an inorganic, biologically compatible material having macro-, meso- and micro-porosity and having a proximal end and a distal end, the proximal end being sealingly closed by a movable plunger; the distal end of the chamber being closed by a dismountable end cap, the end cap being provided with a point for attachment of an aspiration needle; attaching the aspiration needle to the dismountable end cap; placing the aspiration needle into a situs of bone marrow; operating the plunger to draw a partial vacuum in the material chamber and to cause aspiration of bone marrow into the material chamber in an amount sufficient to substantially wet the biologically compatible morselate material; and maintaining the aspirate in contact with the biologically compatible composite under conditions effective to cause at least partial coalescence of the marrow-morselate mixture. In one embodiment, the inorganic material is a highly porous β-TCP material with a pore volume of at least 30% and interconnected micro-, meso-, and macro- porosity; and the biological material is bone marrow aspirate.

[0030] In a further embodiment of the present invention, there is provided a kit for the preparation and delivery of biologically active composites comprising an instrument for the injection and the withdrawal of one or more biological fluids and a porous, biocompatible material wherein the porous, biocompatible material comprises interconnected micro-, meso- and macro-porosity.

[0031] These and other aspects of the invention will be apparent from the following drawings and detailed description of preferred embodiments.

BRIEF DESCRIPTION OF THE DRAWINGS

[0032] Figure 1 is a 100x magnification scanning electron micrograph ("SEM") of an exemplary inorganic substrate material that depicts the macro-, meso- and micro-porosity contained therein.

[0033] Figures 2A and 2B illustrate one embodiment of the porous, biocompatible material of the present invention shaped into a block form and used as a tibial plateau reconstruction that is screwed, bonded, cemented, pinned, anchored, or otherwise attached in place.

[0034] Figure 3 illustrates an embodiment of the porous calcium phosphate scaffolding material preferred in the present invention shaped into a block or sleeve form and used for the repair or replacement of bulk defects in metaphyseal bone, oncology defects or screw augmentation.

[0035] Figure 4 depicts a syringe device for use in infiltrating and delivering the present invention composite.

[0036] Figures 5A and 6B are side elevation and exploded views, respectively, of an exemplary delivery device of the present invention.

[0037] Figures 6A through 6C illustrate an exemplary method of the present invention in which the apparatus of Figures 5A and 5B is used in the following manner: (A) a biological material, such as BMA, is drawn into the device thereby infiltrating the porous substrate material, (B) the plunger is depressed against the congealed mass of material and BMA, and the end piece of the device is removed to provide a biological composite and (C) the biological composite is delivered to an osseous defect site.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[0038] In accordance with the present invention, methods are provided for preparing biologically active composite materials comprising absorbing an infiltrant into at least one porous, biocompatible material; and maintaining the infiltrant and the porous material in contact under conditions effective to achieve at least partial coagulation of the infiltrant and porous material to form a self-supporting body. As used herein, therapeutic materials refer to one or more components of BMA including separated fractions of BMA, venous blood including one or more fractions of venous blood, concentrated platelets, thrombin, growth factors, growth hormones, proteins, genes, antibiotics, and cell signaling materials.

[0039] Representative porous biocompatible materials used in this invention include synthetic bone materials and ceramic materials, which can be made from a variety of calcium phosphate materials. Preferred porous, biocompatible bodies are those obtained generally in accordance with the disclosure of United State Patent Number 5,939,039 filed January 16, 1997, and issued August 17, 1999; and United States Application Number 09/253,556 filed February 19, 1999, now pending, assigned to the assignee of the present invention and incorporated herein by reference. Such bodies preferably exhibit interconnected macro-, meso- and microporosity throughout the bodies.

[0040] The infiltrants can be a number of substances that render the porous material bioactive. In many forms, the infiltrants can comprise therapeutic materials including growth factors or growth hormones that elicit bone formation and reparation. In other forms it may contain medicaments as one of its many ingredients. It may be preferred that the infiltrant contain one or more components of BMA. Bone marrow is a complex tissue comprised of cellular components that contribute to bone growth including red and white blood cells, their precursors and a connective tissue network termed the stroma. Bone

marrow stromal cells or mesenchymal stem cells have the potential to differentiate into a variety of identifiable cell types including osteoblasts, fibroblasts, endothelial cells, reticulocytes, adipocytes, myoblasts and marrow stroma. Consequently, bone marrow aspirate is a good source of osteogenic cells for immediate transplantation. For subsequent use in transplantation, stem cells can also be cultured and expanded to many times their original number. Stromal cells regulate the differentiation of hemopoietic cells through cell-surface protein interactions and secretion of growth factors. Bone marrow has been successfully used to stimulate bone healing in many applications, suggesting a promptly renewable and reliable source of osteogenic cells without the disadvantages of open-grafting techniques. BMA also provides osteoinductive components, namely the progenitors of osteoblasts. Cell progenitors derived from bone marrow can be harvested by aspiration from patients, with limited dilution by peripheral blood if the volume of aspirate from a single site is held to 2 mL or less. Furthermore, the number of progenitors available in a graft site can be increased by concentration if necessary to further enhance the biologic result of bone grafting. Thus, the combination of a tri-calcium phosphate material as described herein with BMA yields a biologically active composite that is osteoconductive and, at least, osteoinductive or osteogenic. The biologically active composite is further rendered osteoinductive and osteogenic since the structure of the tri-calcium phosphate facilitates infusion of bone matrix proteins and growth factors. Osteogenic cells could also migrate into the open architecture of the scaffold and mingle with the seeded bone-forming cells, thereby enhancing the osteogenic properties of the β-TCP.

[0041] In embodiments that may be preferred by some in the art, bone reparation is accomplished by mixing porous bodies containing a polyporous material such as β-TCP

material, with therapeutic material. The materials are allowed to coagulate to form a composite material having an improved handling consistency and osteogenic potential. In another embodiment, the polyporous material is mixed with BMA. Virtually any physical form of β-TCP material can be used, including morsels, blocks, etc. Subsequent to mixing with BMA, and packing in a desired conformation, BMA coagulates over time, thus binding the composite material together. In some embodiments that may be preferred, the coagulation can be for at least five minutes. The bound material behaves as a unit mass and can be surgically implanted by hand or with an instrument. The composite mass can be shaped by application of a gentle force, and/or by cutting. The composite mass can be packed into a bony void to create good contact with available bony surfaces.

[0042] Porous β-TCP synthetic cancellous bone void fillers that are low-density and highly porous resemble human cancellous bone in structure and composition. Generally, β-TCPs contain approximately 39% calcium and 20% phosphorus by weight and have the chemical formula β-$Ca_3(PO_4)_2$. By comparison, natural bone mineral is a carbonate-containing apatite that is approximately 35% calcium and 15% phosphorus. Hence, natural bone mineral and β-TCP are chemically similar. Used as a synthetic bone void filler, β-TCP can be engineered to fill voids or gaps. Blocks of β-TCP can be shaped with a scalpel before being placed into a defect. Additionally, morsels of β-TCP can be packed into an irregularly shaped defect site. When implanted in direct contact with viable host bone, β-TCP facilitates new bone ingrowth (osteoconduction) by serving as a scaffold upon which new bone deposits and matures. The scaffold is then removed by a combination of dissolution and phagocytosis (cell-mediated resorption).

[0043] It will be appreciated that preferred porous biocompatible materials according to the invention exhibit high degrees of porosity over a wide range of effective pore sizes. In

this regard, such porous bodies preferably have, at once, macroporosity, mesoporosity and microporosity as depicted in Figure 1. Macroporosity is characterized by pore diameters greater than about 100 μm. Mesoporosity is characterized by pore diameters between about 100 and 10 μm, while microporosity occurs when pores have diameters below about 10 μm. It is preferred that macro-, meso- and microporosity simultaneously occur in a random and interconnected nature throughout the porous material used in the invention. It is not necessary to quantify each type of porosity to a high degree. Rather, persons skilled in the art can easily determine whether a material has each type of porosity through examination, such as through methods of scanning electron microscopy or mercury porosimetry.

[0044] In some embodiments that may be preferred, the porous materials can have pore volumes of at least about 30%. In other typical embodiments, the porous materials can have pore volumes of at least about 70%, more preferably in excess of about 85%, with 90% being still more preferred. In preferred cases, such high pore volumes are attained while also attaining the presence of macro-, meso- and micro-porosity as well as physical stability of the materials produced. In one typical embodiment of the invention, the porous biocompatible material is an osteoconductive tri-calcium phosphate material with interconnected micro, meso and macro-pores, which, together, impart a pore volume of at least 90% to the porous material. It is believed to be a great advantage to be able to prepare inorganic shaped bodies having interconnected macro-, meso- and micro-porosity with high pore volumes to permit more thorough infiltration of therapeutics, a more continuous supply of nutrients, more extensive cellular and tissue ingrowth into the scaffold, and enhanced revascularization, allowing bone growth and repair to take place more efficiently.

[0045] The present invention has utility in a wide variety of applications. The porous shaped bodies can be used in medicine, for example, for the restoration of bony defects and the like. The materials can also be used for the delivery of healing materials, such as medicaments, internal to the body. When used with medicaments, the porosity of a material formed in accordance with the invention can be all or partially filled with another material, which either comprises or carries the medicaments. Indeed, the larger porous spaces within some of the products of the present invention can be used for the culturing of cells within the human body. In this regard, the larger spaces are amenable to the growth of cells and can be permeated readily by bone cells and bodily fluids such as certain blood components. Growing cells can also be implanted in an animal through the aegis of implants in accordance with the present invention. The implants described herein can give rise to important biochemical or therapeutic or other uses.

[0046] The methods of the present invention can further include an absorbing step comprising aspirating therapeutic material onto the porous material. The aspirating step can comprises drawing bone marrow into a body of a syringe at least partially containing the porous material. The maintaining step, which can takes place within a syringe, further comprises extruding the self-supporting body. Some skilled in the art may choose to manipulate the self-supporting body as part of one of the methods disclosed. Many methods can further comprise adding a healing composition, such as a medicament, to the self-supporting body or to the porous material. In other methods, the infiltrant can consist of bone marrow aspirate.

[0047] Figure 2A depicts a plug of the porous, calcium phosphate scaffolding material 80. Figure 2B illustrates plug 80, which is inserted into an excavation site 83 within a human knee, below the femur 81 and above the tibia 82, for use in a tibial plateau reconstruction.

Plug 80 is held in place or stabilized via a bone cement layer 84. In the present invention, plug 80 is imbibed with an infiltrant prior to insertion for reparation, as disclosed herein.

[0048] Figure 3 shows the calcium phosphate scaffolding material within a human femur that is used as a block 92 for bulk restoration or repair of bulk defects in metaphyseal bone or oncology defects, or as a sleeve 94 for an orthopaedic screw, rod or pin 98 augmentation. Item 99 depicts an orthopaedic plate anchored by the orthopaedic device item 98. Bone cement layer 96 surrounds and supports sleeve 94 in place. In the present invention, a block 92 is imbibed with an infiltrant prior to insertion for reparation, as disclosed herein.

[0049] In accordance with this invention, methods are provided for restoring an osseous void comprising placing in said void at least a portion of a self-supporting body comprising partially coagulated infiltrant in admixture with a porous, biocompatible material. In one embodiment that may be preferred, the composites used to fill the void are comprised of a porous biocompatible material imbibed throughout its structure with an infiltrant or therapeutic material for a predetermined period of coagulation. The resultant composite is sufficiently self-supporting to be handled with surgical hand tools such as spatulas and knives. The composite need not be entirely stiff but can tend to flow under force. Typically, a shapeable portion of the composite can be placed into a bone void. The shaping of the composite can take place before placing it into the osseous void or performed while in the void. Any remaining composite can be preserved in a freezer or other suitable means of preserving.

[0050] The placement of the self-supporting body can be effected using a syringe. In many other embodiments the placement may be effected using a tube, insertion guide, catheter or shaped mold.

[0051] The tri-calcium phosphate in the many embodiments of the present invention is resorbable. Resorption of calcium-based bone implants is influenced largely by the composition, physical structure and solubility of the implant. The porous bodies that may be preferred in some embodiments of the present invention have significant resorption due to their low density, high porosity, nano-size particle composition, and chemistry. As calcium-based implants are resorbed, they are often replaced by new bone. Porous tri-calcium phosphate bone implants can resorb more quickly than porous hydroxyapatite. The porous tri-calcium phosphate resorption rate is concurrent with the rapid rate of ingrowth and remodeling of new bone.

[0052] The present invention can call for the use of therapeutic materials or any mixture of materials therein, as an alternative to BMA or in conjunction therewith. Replicated bone marrow or other types of bioengineered bone marrow material can be used in this invention. Exemplary therapeutic materials include signaling molecules under the Transforming Growth Factor (TGF) Superfamily of proteins, specifically proteins under the TGF-beta (TGF-β), Osteogenic Protein (OP)/Bone Morphogenic Protein (BMP), VEGF (VEGF-1 and VEGF-2 proteins) and Inhibin/activtin (Inhibin-beta A, Inhibin-beta B, Inhibin-alpha, and MIS proteins) subfamilies. Most preferably, the exemplary therapeutic materials are proteins under the TGF-β and OP/BMP subfamilies. The TGF-β subfamily includes the proteins Beta-2, Beta-3, Beta-4 (chicken), Beta-1, Beta-5 (xenopus) and HIF-1 alpha. The OP/BMP subfamily includes the proteins BMP-2, BMP-4, DPP, BMP-5, Vgr-1, OP-1/BMP-7, Drosophila 60A, GDF-1, Xenopus Vg-1 and BMP-3. Representative proteins of these types include: OP-1/rhBMP-7 (Stryker Corporation, Kalamazoo, MI), rhBMP-2 (Genetics Institute/American Home Products, Madison, NJ), IGF-1 (Insulin-like Growth Factor-1) (Cephalon, West Chester, PA), TGF beta

(Genentech, San Francisco, CA), MP52 (Biopharm GmbH, Heidelberg, Germany). Other proteins, genes and cells outside the TGF Superfamily may also be included in the exemplary types of therapeutic materials to be used in conjunction with the present invention. These other proteins, genes and cells include PepGen P-15 (Ceramed, Lakewood, CO), LMP-1 (LIM Mineralized Protein-1 gene) (Emory University, Atlanta, GA/Medtronic Sofamor Danek, Minneapolis, MN), Chrysalin TP 508 Synthetic Peptide (Chrysalis Biotechnology, Galveston, TX), GAM (parathyroid hormone) (Selective Genetics, San Diego, CA), rhGDF-5 (Orquest, Mountain View, CA), cell lines and FGF (Fibroblast Growth Factor) such as BFGF (Basic Fibroblast Growth Factor), FGF-A (Fibroblast Growth Factor Acidic), FGFR (Fibroblast Growth Factor Receptor) and certain cell lines such as osteosarcoma cell lines. The therapeutic materials to be used with the present invention material may also be combinations of those listed above. Such mixtures include products like Ne-Osteo GFm (growth factor mixture) (Sulzer Orthopaedics, Austin, TX), or mixtures of growth factors/proteins/genes/cells produced by devices such as AGF (Autologous Growth Factor) (Interpore Cross International, Irvine, CA), Symphony Platelet Concentrate System (Harvest Technologies, Belton, TX/DePuy, Warsaw, IN), and the like.

[0053] According to the present invention, there are methods for restoring an intraosseous void comprising preparing said void; providing an aspirating means having porous material therein; aspirating bone marrow from an animal using the aspirating means; allowing BMA to mix with the porous material, thereby producing a composite of said aspirate and said porous material; allowing said aspirate to at least partially coagulate; removing the said composite from the aspirating means; and placing at least a portion of said composite into said void.

[0054] A syringe can be used as an aspirating means for the porous materials. Also well suited as an aspirating means is a shaped mold, catheter tube, insertion guide or the like. The resultant composites of the present invention can be saved for later use. They can also be preserved by a variety of methods known in the art including freezing.

[0055] The methods of the present invention give rise to kits that are unique in their ability to prepare and deliver the biologically active composite. A preferred embodiment is made of a syringe capable of holding porous, biocompatible material. The syringe is used to prepare the composite when a therapeutic such as BMA is absorbed into the porous material by the aspiration process. A typical syringe device is shown in Figure 4. The composite is formed within the barrel 20 of the syringe once the aspirate coagulates with the porous material 120. The syringe used can be of varying volumes, shapes and cross sections. The same syringe can be used to deliver the resultant composite by removing the end portion and extruding the composite to be placed into an osseous void.

[0056] It will be appreciated that a number of surgical devices can be used to aspirate bone marrow. In other embodiments a shaped mold, catheter tube, insertion guide and the like can be used to aspirate. Coagulation also need not take place in the body of any of these devices but may be transferred to another container. The composite can then be removed and sculpted using a scalpel or other instrument before placement into a void. The composite can already be formed by virtue of the shape of the container chosen.

[0057] As will be appreciated, other forms of surgical devices can be used in addition to a syringe, and each device can be housed as part of a kit. In this manner, a number of syringes can be included in the kit. In one embodiment of the present invention a small 1 cc syringe is used to aspirate the bone marrow and to deliver the aspirate into a second syringe, container or mold holding the porous material. Some kits can also include a pre-

evacuated tube to aspirate bone marrow. Other kits can be expanded further by including cutting instruments, such as a scalpel or knife, and other surgical hand tools used to shape and mold the composite, such as a spatula.

[0058] The present invention relates to an apparatus for the delivery of a biological composite that houses a substrate material, allows for the substrate material to be rendered biologically active to form a biological composite, and facilitates delivery of the biological composite to an osseous defect site. Preferably, the substrate material is a highly porous β-TCP with a pore volume of at least 30% and interconnected porosity of pore sizes that may range from less than about 10 μm to about 100 μm or greater.

[0059] Figures 5A, 5B and 4 provide one example of a presently preferred embodiment of the present invention. As these figures illustrate, apparatus 10 comprises a material chamber 20 having a proximal end 21 and a distal end 22 defining an interior chamber therein for housing a porous substrate as shown as 120 in Figure 4. In certain embodiments, material chamber 20 may be tubular or cylindrical shaped. Preferably, material chamber 20 may have external calibration markings 30 (see Figure 5A) to measure the amount of material housed, drawn into, or aspirated within or into material chamber 20. Apparatus 10 may further include a piston or gasket 40, as shown in Figures 5B and 4, which may reside within the material chamber 20 and is moveable therein via engaging plunger 50 attached thereto. Plunger 50 is removable from the housing to allow for material insertion within the material chamber 20, or the injection of any desired material, such as biologic material, into chamber 20.

[0060] The distal end 22 of apparatus 10 is provided with a removable dismountable end cap 60 with a proximal end 61 having threads, guides, slots, or other structures for engaging corresponding threads, guides, slots or other structures on the distal end 22 of

the material chamber 20. Dismountable end cap 60 further includes a distal end 62 with a point for attachment 63 of an aspiration needle 110. In a preferred embodiment, the point for attachment 63 is a male Luer lock connector 90 that threadingly engages the distal end 62 of the dismountable end cap 60 and allows for attachment of a female Luer lock 100 situated on the end of a needle 110 for the aspiration of fluids. In other embodiments of the present invention, the male Luer lock connector 90 is integrated with the distal end 63 of the dismountable end cap 60 (not shown). An adhesive, such as but not limited to a polyurethane adhesive, may also be used between dismountable end cap 60 and Luer lock connector 90 to form an integrated piece. An exemplary polyurethane adhesive is Product #1187-M provided by Dymax Corporation of Torrington, Ct.

[0061] As shown in Figure 4, material chamber 20 further includes a substrate material 120 contained therein. Substrate material 120 may be comprised of a variety of synthetic biocompatible bone materials and ceramic materials, including, but not limited to, those comprising calcium phosphate. Material 120 may be in a variety of forms such as an integral body of porous material, granules, or morsels. Preferred biocompatible materials are those obtained generally in accordance with the disclosure of pending application, U. Patent No. 5,939,039, issued August 17, 1999, assigned to the assignee of the present invention and incorporated herein by reference in its entirety. Such beta-tricalcium materials exhibit a high degree of porosity over a wide range of effective pore sizes.

[0062] In embodiments where substrate material 120 is an integral body of porous material, the body preferably exhibits within its microstructure, a combination of macro-porosity, meso-porosity, and micro-porosity. Macro-porosity, as used herein, relates to materials characterized by pore diameters about 100 μm or greater, and more preferably up to about 1000 μm. Meso-porosity, as used herein, relates to materials characterized by

pore diameters that range from about 10 μm to about 100 μm. Micro-porosity, as used herein, relates to materials characterized by pore diameters below about 10 μm, and more preferably about 1 μm or below. Figure 1 provides a SEM of the microstructure of a preferred substrate material that may be used in the present invention. It is preferred that macro-, meso- and micro-porosity simultaneously occur in a random and interconnected nature throughout the porous substrate material used in the present invention. It is not necessary to quantify each type of porosity to a high degree. Rather, persons skilled in the art can easily determine whether a material has each type of porosity through examination, such as through the SEM or other methods known in the art.

[0063] In addition to the interconnected range of pore sizes, porous substrate material 120 may have pore volumes of at least about 30% or greater, preferably about 85% or greater, and even more preferably about 90% or greater. Such high pore volumes may be achieved while also maintaining the presence of macro-, meso-, and micro-porosity within the microstructure and physical stability of the materials produced. These aspects of the porous substrate material are desirable for use within the apparatuses, kits, systems, and methods of the present invention in that they facilitate wicking of the biological material and infiltration of the viable components of the biological fluid.

[0064] In a preferred embodiment of the present invention, the apparatus is used to prepare a biological composite using the method and kit depicted in Figures 6A, 6B and 6C. As these figures illustrate, plunger 50 or dismountable end cap 65 is removed from apparatus 10 and the biocompatible material 120 is inserted into material chamber 20. Dismountable end cap 65 is an integral piece that comprises Luer lock connector 95. Luer lock mating means 105 with needle attachment 110 may be connected thereto. Plunger 50 is then reinserted into, or dismountable end cap 65 is placed back onto, material chamber

20. Piston 40 is dispaced so that it abuts and lightly packs the material (not shown). The tip of the biopsy needle 110 is then inserted into an appropriate anatomical site 130, such as for example the iliac crest. Biopsy needle 110 preferably has a solid trochar (not shown). The syringe is then connected to needle 110 via the Luer lock mating means 105 and connector 95. Withdrawal of the plunger creates a vacuum within the housing 20, which allows for the biological fluid to be drawn into the housing of the device as shown in Figure 6A. The fluid completely imbibes and infiltrates the biocompatible material 120, once in contact with the material, by virtue of its highly porous and interconnected porosity. The plunger is depressed so that it abuts and compacts both the material and infiltrate so that the two are allowed to coagulate within the housing to form a biological composite 140 having an improved handling consistency and osteogenic potential. As Figure 6B shows, the resulting composite 140 behaves as a unit mass and can be surgically implanted via displacement of the plunger 50, upon removal of the dismountable end cap 65. A wrench (not shown) may be used that mates with dismountable end cap 65 to aid in opening and closing the syringe. In other embodiments of the method of the present invention, material chamber 20 may be pre-filled with BMA or another biocompatible material and dismountable end cap 60 or plunger 50 may be removed to insert substrate material 120.

[0065] The composite 140 can be packed into a bony void to create good contact with available bony surfaces. The resultant composite is sufficiently self-supporting to be handled manually or with surgical hand tools such as spatulas and knives. The composite need not be entirely stiff but can tend to flow under force. Preferably, a shapeable portion of the composite is placed into a void 150 in a bone 160 as shown in Figure 6C. Any

remaining biological composite 140 can be preserved in a freezer or other suitable means of preserving.

[0066] The present invention also gives rise to a method and a kit that is unique in its ability to prepare and deliver the biologically active composite. A preferred kit embodiment is comprised of an apparatus or delivery device capable of holding porous, biocompatible material as described herein and a separate sterile package holding the inorganic material. The kit is used to prepare a biologically active composite wherein BMA or other infiltrant is absorbed into the porous material by the aspiration process. The composite is formed within the barrel of the syringe once the aspirate coagulates with the porous material. The same kit can be used to deliver the resultant composite by removing the end of the syringe and extruding the composite to be placed into an osseous void.

[0067] The materials, which comprise the syringe, can a variety of standard polymeric materials used in the field. For instance, the material chamber or barrel and threaded dismountable end cap may be comprised of a polycarbonate material, such as that sold by Dow, 2081-15-FC030004; the plunger may be comprised of acrylonitrile-butadiene-styrene (such as the Dow Magnum 9010 material); the piston or gasket may be comprised of a silicone-64 Shore A durometer base material, such as the blend of STI-5 and TR-70 sold by Dow Corning; a lubricant between the inside of the barrel and the plunger piston is preferably silicone oil (such as Dow Corning Silicone 360); and the adhesive on the threaded coupling between the Luer lock and dismountable end cap may be medical grade silicone or a number of acceptable adhesives including, but not limited to, cyanoacrylate, hot melt adhesives, or cellulosic binders. Alternatively, the the Luer lock and

dismountable end cap may be connected via ultrasonic welding, spin welding, or insert molding rather than the use of adhesive.

[0068] Additional objects, advantages, and novel features of this invention will become apparent to those skilled in the art upon examination of the following examples thereof, which are not intended to be limiting.

EXAMPLES

Example 1 - Healing of Tibial Segmental Defects in Dogs Using Biologically Active Composites

[0069] Thirty-five vials of a porous, biocompatible material such as VITOSS™ Scaffold Synthetic Cancellous Bone Void Filler morsels (provided by Orthovita of Malvern, PA), referred to herein as "Test Article", were prepared and assigned a unique identification number for the study. Table I provides the animal subjects' ID number, test article ID numbers, amount of biological material imbibed into the VITOSS porous scaffold material, and the amount in grams of residual VITOSS and BMA composite.

Animal ID	Test Article ID	Amount Mixed (g)	Residual VITOSS™/BMA (cc)
11A	ORL-131-T	0.72	0.9
11B	ORL-101-T	0.54	0.3
11C	ORL-117-T	0.72	1.0
11D	ORL-131-T	0.80	0.7
11E	ORL-109-T	0.37	0.4
12A	ORL-134-T	0.79	N/A
12B	ORL-119-T	1.04	N/A

12C	ORL-101-T	1.21	N/A
12D	ORL-109-T	0.45	N/A
12E	ORL-127-T	1.15*	3.0*
13A	ORL-113-T	0.76	0.2
13B	ORL-113-T	0.85	0.3
13C	ORL-119-T	0.77	N/A
13D	ORL-118-T	0.94	0.3
13E	ORL-131-T	0.88	0.6
14A	ORL-134-T	0.86	0.3
14B	ORL-118-T	1.61*	N/A*
14C	ORL-100-T	0.93	N/A
14D	ORL-133-T	0.79	N/A
14E	ORL-133-T	0.97	N/A
15A	ORL-113-T	0.79	N/A
15B	ORL-134-T	0.83	0.4
15C	ORL-133-T	0.75	0.1
15D	ORL-131-T	0.84	0.5
15E	ORL-109-T	0.74	N/A
16A	ORL-134-T	0.73	N/A
16B	ORL-119-T	0.81	N/A
16C	ORL-117-T	0.75	N/A
16D	ORL-117-T	1.05	N/A
16E	ORL-127-T	0.90	N/A

* An additional quantity of VITOSS/BMA was prepared for use if necessary.

[0070] Surgical procedures were scheduled in "sessions", with three surgical procedures typically performed per session. Prior to the start of each surgery session, a vial of Test Article was removed from the sterile packaging for use during the entire session. Care was taken to maintain sterility of the vial throughout the session.

[0071] While maintaining sterility, each vial of Test Article was weighed prior to and following removal of material for placement in each Test System. The total amount of Test Article used in each Test System was determined in this way.

[0072] Prior to the first surgical procedure, the method for preparing and mixing the Test Article was determined in detail. The method, as described in Protocol Amendment 4, is as follows:

1. A 5 cc syringe was filled to the 4cc mark with Test Article.
2. The syringe was tapped to settle the Test Article.
3. The syringe plunger was then compressed to the 3 cc mark.
4. The syringe containing the Test Article was attached to the needle being used for BMA collection.
5. BMA was either: (1) drawn into the syringe through the Test Article such that it completely saturated it; or (2) drawn into a 1 cc syringe and then transferred to the 5 cc syringe containing the VITOSS™ scaffold material such that the BMA completely saturated it. In some cases, the syringe was removed to withdraw air and reattached.
6. Following saturation, the plunger was compressed to the 3 cc mark.
7. The syringe containing the mixture was allowed to sit for at least 5 minutes.

8. The tip was removed from the syringe so that the mixture could be removed.

9. The mixture was placed into the defect and finger packed.

Thirty animals underwent an identical surgical procedure. Surgery was performed in accordance with the following study protocol. The experimental hind limb was prepped and draped in standard sterile fashion. The lilac crest was exposed laterally through a 2 cm or smaller skin incision and BMA was collected using a 13 or 15 gauge Jamshidi needle and syringe. The BMA was then mixed with the VITOSS to provide a biological composite. At least 3 cc of BMA was collected from the animal for mixing. The amount of VITOSS scaffold material that was mixed with the BMA is provided in Table I.

[0073] Following closure of the marrow harvest site, a four-pin, Type 1 Kirschner external fixator was placed on the anterio-lateral aspect of the experimental tibia. A medial skin incision approximately 3 cm in length was made and exposure of the tibia was obtained using sharp and blunt dissection. Once exposed, the periosteum was scored and reflected back. The major axis of the mid-section of the tibia was then measured. A cortical segmental defect approximately two times the mid-shaft major axis dimension was created in the mid-tibia using an oscillating saw. The defect was then completely filled with VITOSS™ and the periosteum closed with non-absorbable suture to contain it. The residual amount of remaining biological composite after the defect was filled is shown in Table I. The soft tissues were closed in layers.

[0074] Those skilled in the art will appreciate that numerous changes and modifications may be made to the preferred embodiments of the invention and that such changes and modifications may be made without departing from the spirit of the invention. It is

therefore intended that the appended claims cover all such equivalent variations as fall within the true spirit and scope of the invention.

[0075] A kit of the present invention for the aspiration of bone marrow, whole blood, plasma or other blood components was evaluated using a non-human primate animal model. The kit was evaluated for collection of bone marrow and venous blood, with and without a highly porous calcium phosphate scaffold material, in the following manner.

[0076] A single skeletally mature baboon was anesthetized for the duration of the study using isoflurane inhalation.

[0077] A 20-gauge needle was affixed to a male Luer-lock adaptor situated on the end of the syringe system. An 18-gauge catheter was placed in the right lateral saphenous vein of the animal for repeated blood collection, then the 20 gauge needle was placed in contact with the 18 gauge catheter for collection of venous blood. The ability of the syringe system to draw blood was subjectively evaluated with and without the addition of 5 cc of a morselate calcium phosphate material in the material chamber of the syringe. This evaluation was compared a Luer Lock 10 cc disposable syringe, manufactured by the Becton Dickinson Co. of Rutherford, N.J., with the addition of 5 cc of the morselate calcium phosphate material described above.

[0078] Following venous blood collection, the syringe system was evaluated during harvest of bone marrow aspirate from the posterior superior iliac spine region of the right ileum using an 11-gauge Jamshidi needle was placed directly in the site the syringe system was and then attached for aspiration. The ability of the syringe system to aspirate bone marrow was subjectively evaluated with and without the addition of 5 cc of a morselate calcium phosphate material in the material chamber of the syringe.

[0079] The syringe system, both with and without the addition of 5 cc of a morselate calcium phosphate material in the material chamber, was sufficient for both collection of venous blood and the harvest of bone marrow aspirate. Adding the porous material to the chamber had no effect on the ability of the system to draw blood or aspirate marrow. The vacuum that was generated in each case was sufficient. There were no differences between a first draw of blood with the syringe system in comparison with a second draw from the same syringe.

WHAT IS CLAIMED IS:

1. A method for preparing a biologically active composite material comprising:

-absorbing an infiltrant into at least one porous, biocompatible material; and

-maintaining the infiltrant and the porous material in contact under conditions effective to achieve at least partial coagulation of the infiltrant to form a self-supporting body.

2. The method of claim 1 wherein said porous, biocompatible material has a pore volume of at least about 30%.
3. The method of claim 1 wherein said porous, biocompatible material has a pore volume of at least about 70%.
4. The method of claim 1 wherein said porous, biocompatible material has a pore volume of at least about 85%.
5. The method of claim 1 wherein said porous, biocompatible material has a pore volume of at least about 88%.
6. The method of claim 1 wherein the porous, biocompatible material has a pore volume more of at least about 90%.
7. The method of claim 1 wherein the porous, biocompatible material is selected from the group consisting of a synthetic bone mineral, a ceramic material, a calcium phosphate material and a tri-calcium phosphate material.
8. The method of claim 7 wherein the tri-calcium phosphate material is beta-tri-calcium phosphate.
9. The method of claim 1 wherein the porous material is resorbable.
10. The method of claim 1 wherein the at least one porous, biocompatible material is comprised of a resorbable beta-tri-calcium phosphate with interconnected micro-,

meso- and macro-pores that render said at least one porous, biocompatible material at least about 90% porous.

11. The method of claim 1 wherein said absorbing step comprises aspirating therapeutic material onto the porous material.

12. The method of claim 11 wherein said aspirating step comprises drawing bone marrow into a body of a syringe at least partially containing the porous material.

13. The method of claim 1 further comprising adding a medicament to the self-supporting body or to the porous material.

14. The method of claim 1 wherein said infiltrant is selected from the group consisting of bone marrow aspirate, venous blood., thrombin, proteins, cells, growth factors or growth hormones that elicit bone formation or reparation.

15. A method for restoring an osseous void comprising placing in said void at least a portion of a self-supporting body comprising partially coagulated infiltrant in admixture with a porous, biocompatible material.

16. The method of claim 15 wherein said portion is shaped to fit said void.

17. The method of claim 15 wherein placement is effected using a syringe, tube, insertion guide, catheter, or shaped mold.

18. The method of claim 15 wherein the infiltrant is selected from the group consisting of replicated bone marrow, bone marrow aspirate, proteins, cells, a medicament, growth factors, growth hormones or antibiotics that would elicit bone formation or reparation.

19. The method of claim 15 wherein the porous, biocompatible material is selected from the group consisting of a synthetic bone mineral, a ceramic material, calcium phosphate material and a tri-calcium phosphate material.

20. The method of claim 19 wherein the tri-calcium phosphate material is beta-tri-calcium phosphate.

21. The method of claim 15 wherein the porous, biocompatible material is resorbable.

22. The method of claim 15 wherein the infiltrant comprises venous blood or thrombin.

23. The method of claim 15 wherein the porous, biocompatible material has a pore volume of at least about 30%

24. The method of claim 15 wherein the porous, biocompatible material has a pore volume of at least about 70%.

25. The method of claim 15 wherein the porous, biocompatible material has a pore volume of at least about 85%.

26. The method of claim 15 wherein said porous, biocompatible material has a pore volume of at least about 88%.

27. The method of claim 15 wherein the porous, biocompatible material has a pore volume more of at least about 90%.

28. The method of claim 15 wherein the at least one porous, biocompatible material is comprised of a resorbable beta-tri-calcium phosphate with interconnected micro-, meso- and macro-pores that render said at least one porous, biocompatible material at least about 90% porous.

29. A method for restoring an intraosseous void comprising:

- preparing said void;
- providing a syringe having porous material therein;
- aspirating bone marrow from an animal using said syringe, thereby producing a composite of said aspirate and said porous material;
- allowing said aspirate to at least partially coagulate;

- removing the said composite from the syringe; and
- placing at least a portion of said composite into said void.

30. The method of claim 29 wherein resultant composite is delivered into said void by syringe.

31. The method of claim 29 wherein the aspirate is allowed to coagulate for at least five minutes.

32. The method of claim 29 further comprising preserving any remaining resultant composite for later use.

33. The method of claim 29 wherein preservation is by freezing.

34. The method of claim 29 wherein the porous material is comprised of a resorbable beta-tri-calcium phosphate with interconnected micro, meso and macro pores that render said porous biocompatible material at least about 90% porous.

35. A biologically active composite comprising a porous, biocompatible material and infiltrant.

36. The biologically active composite of claim 35 wherein the infiltrant is selected from the group consisting of bone marrow aspirate, venous blood and thrombin.

37. The biologically active composite of claim 35 wherein the porous material has pores with a diameter up to about 100 μm.

38. The biologically active composite of claim 35 wherein the porous, biocompatible material has a pore volume of at least about 30%.

39. The biologically active composite of claim 35 wherein the porous, biocompatible material has a pore volume of at least about 70%.

40. The biologically active composite of claim 35 wherein the porous, biocompatible material has a pore volume preferably of at least about 85%.

41. The biologically active composite of claim 35 wherein the porous material has a pore volume preferably of at least about 88%.

42. The biologically active composite of claim 35 wherein the porous material has a pore volume more preferably of at least about 90%.

43. The biologically active composite of claim 35 wherein the porous material is selected from the group consisting of a synthetic bone mineral, a ceramic material, a calcium phosphate material and a tri-calcium phosphate material.

44. The biologically active composite of claim 43 wherein the tri-calcium phosphate material is resorbable beta-tri-calcium phosphate.

45. The biologically active composite of claim 35 wherein the at least one porous, biocompatible material is comprised of a resorbable beta-tri-calcium phosphate with interconnected micro-, meso- and macro-pores that render said at least one porous, biocompatible material at least about 90% porous.

46. The biologically active composite of claim 35 wherein the infiltrant comprises proteins, cells, a medicament, antibiotic, growth factor, or growth hormone that elicit bone formation or reparation.

47. An apparatus for preparing a biological composite, comprising:

- a material chamber, having a proximal end and a distal end, and comprising a calcium phosphate material having macro-, meso- and micro-porosity, the proximal end being sealingly closed by a movable plunger; and
- the distal end of the chamber being closed by a dismountable end cap, the end cap being provided with a point for attachment of an aspiration needle.

- operating the plunger to draw a vacuum in the material chamber and to cause aspiration of bone marrow into the material chamber in an amount sufficient to substantially wet the biologically compatible material to form a biologically compatible composite; and
- maintaining the aspirate in contact with the biologically compatible composite under conditions effective to cause at least partial coalescence of the marrow within the composite.

56. The method of claim 55 wherein said inorganic, biologically compatible material has a pore volume of at least 85%.

57. The method of claim 55 wherein said inorganic, biologically compatible material has a pore volume of at least 88%.

58. The method of claim 55 wherein the inorganic, biologically compatible material has a pore volume more of at least 90%.

59. The method of claim 55 wherein the inorganic, biologically compatible material is selected from the group consisting of a ceramic material, a calcium phosphate material and a tri-calcium phosphate material.

60. The method of claim 59 wherein the tri-calcium phosphate material is a beta-tri-calcium phosphate.

61. The method of claim 55 wherein the inorganic, biologically compatible material is resorbable.

62. A kit for preparation and delivery of biologically active composites comprising:

- an instrument for the injection and the withdrawal of one or more biological fluids; and

- a porous, biocompatible material wherein the porous, biocompatible material comprises interconnected micro-, meso- and macro-porosity.

63. A kit of claim 62 wherein the instrument for said injection and said withdrawal of said fluids is a syringe or pre-evacuated tube.

64. The kit of claim 62 wherein the porous, biocompatible material comprises a beta-tri-calcium phosphate.

65. The kit of claim 62 wherein the porous, biocompatible material is at least 90% porous.

66. The kit of claim 62 wherein said porous, biocompatible material is in morsel form or block form.

67. The kit of claim 62 further comprising a cutting instrument.

68. The kit of claim 62 further comprising a spatula.

FIG. 1

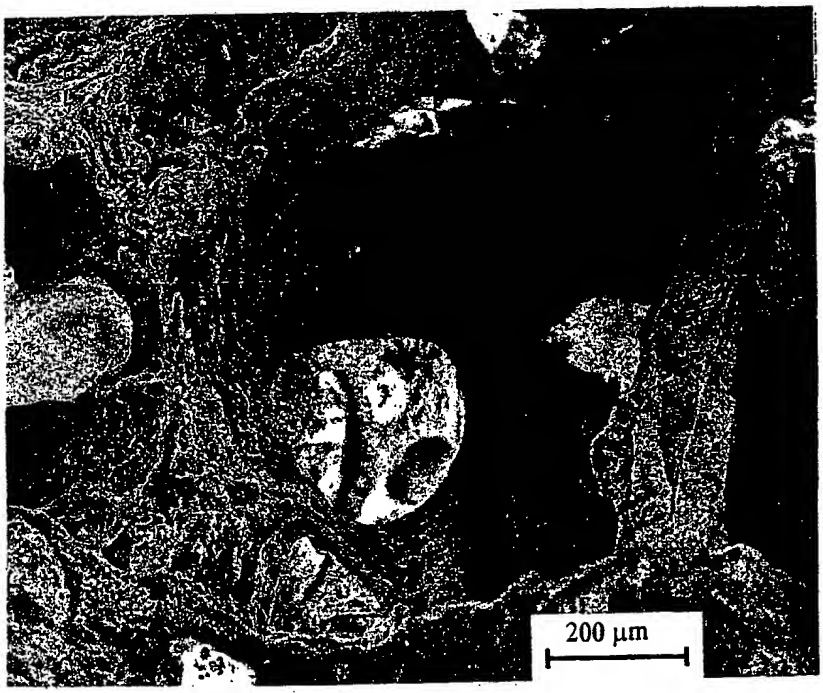

FIG. 2A

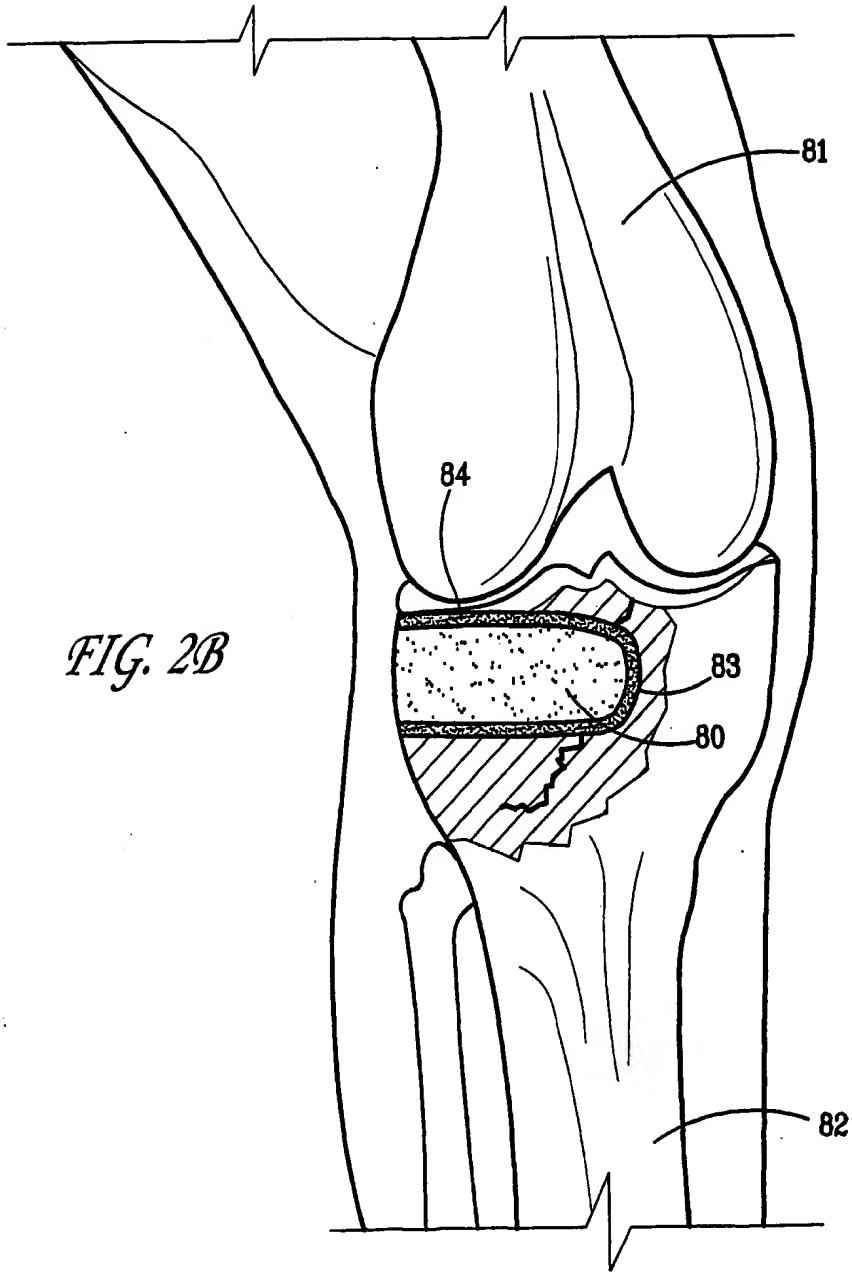

FIG. 2B

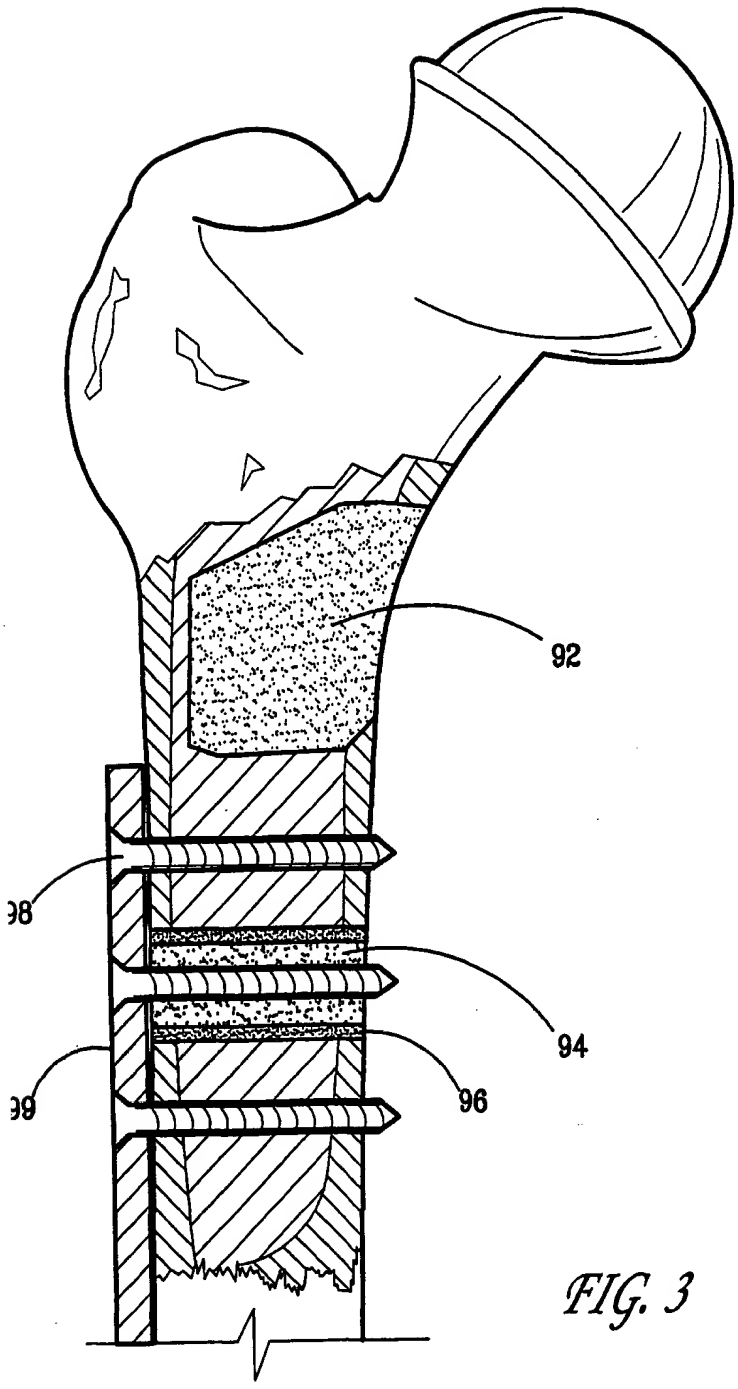

FIG. 3

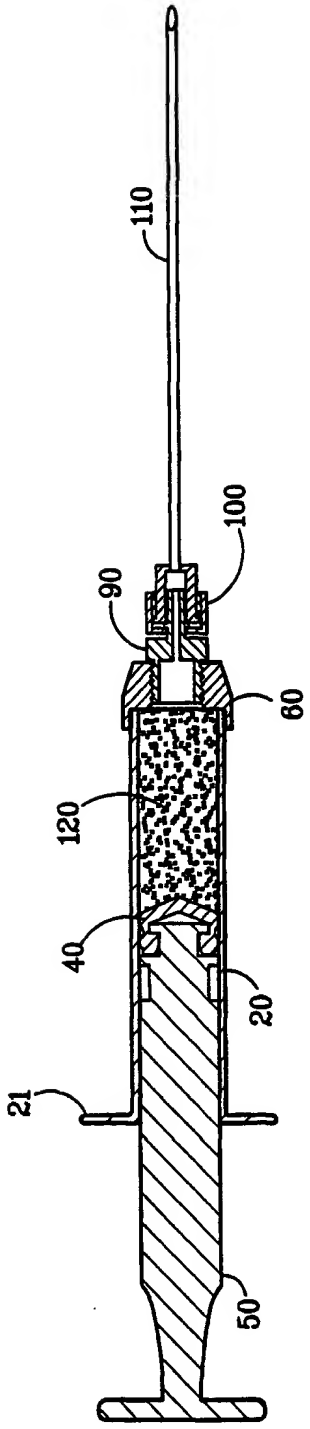

FIG. 4

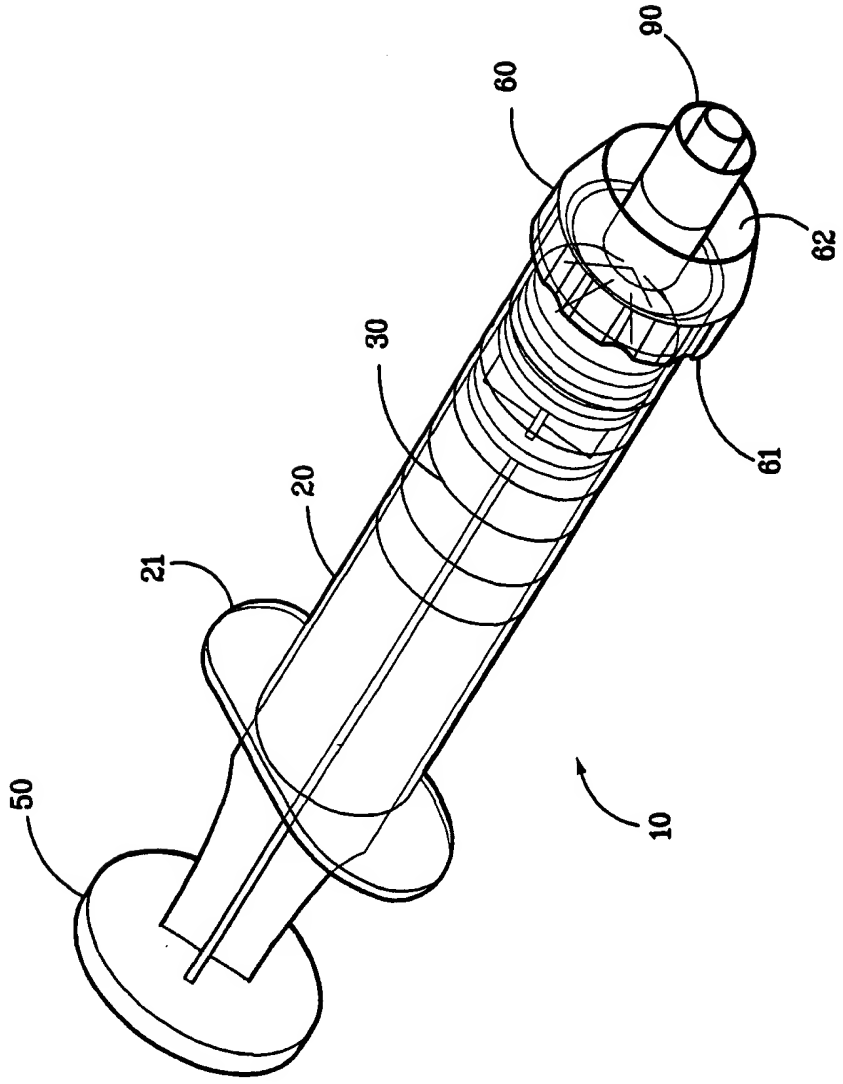

FIG. 5A

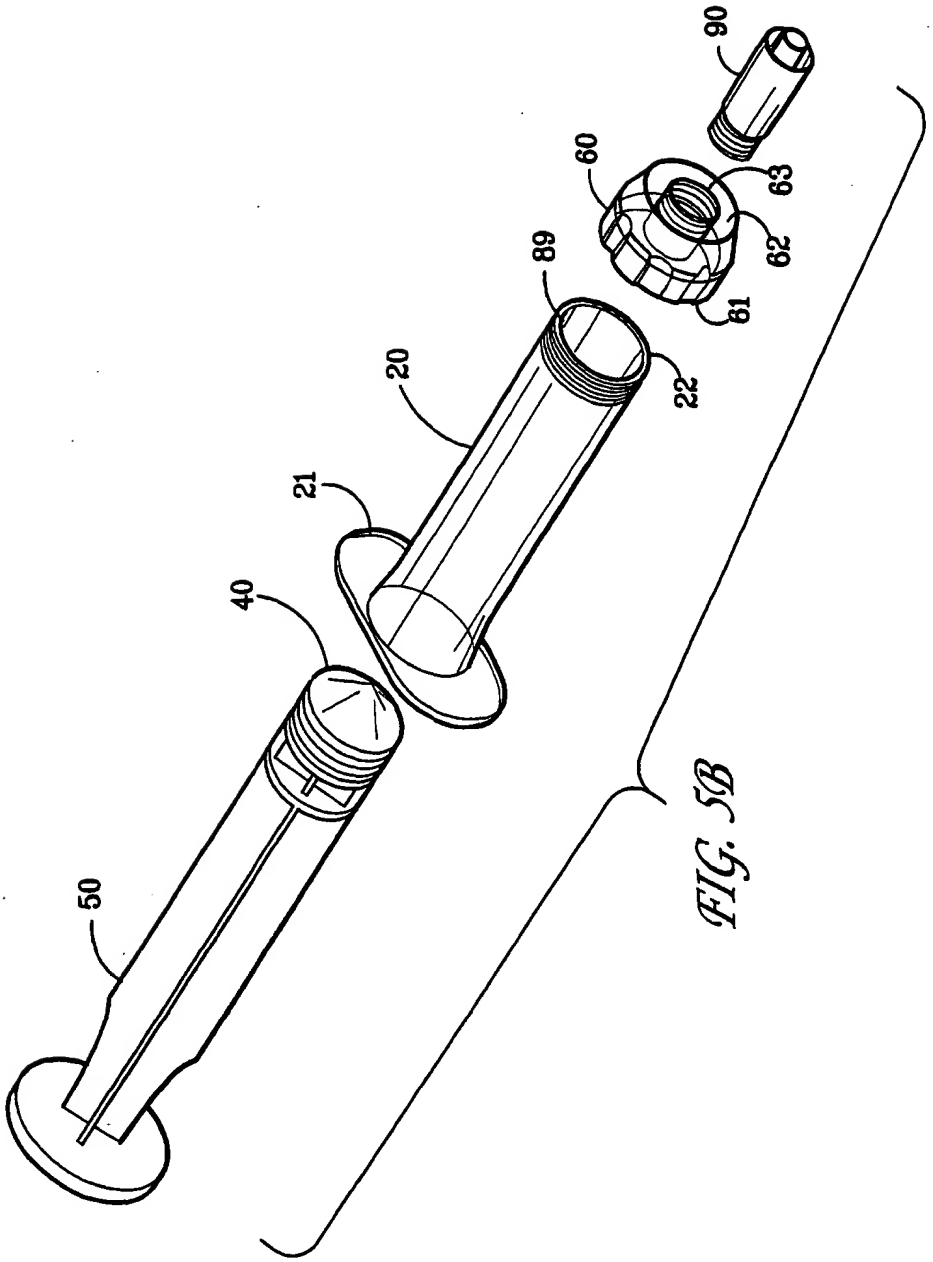

FIG. 5B

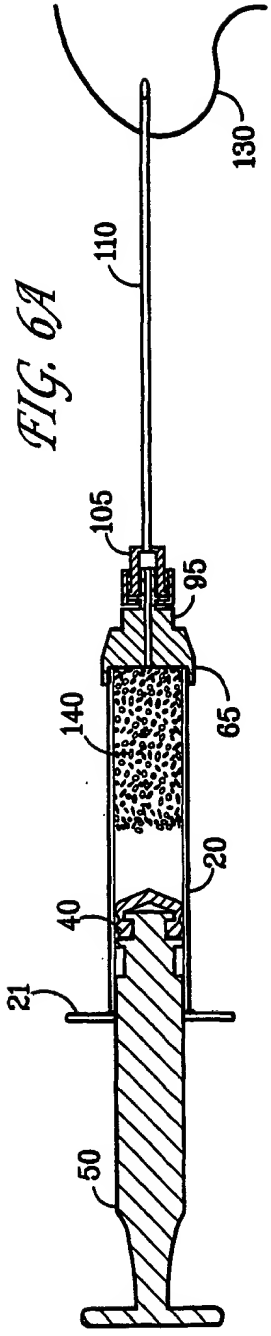

FIG. 6A

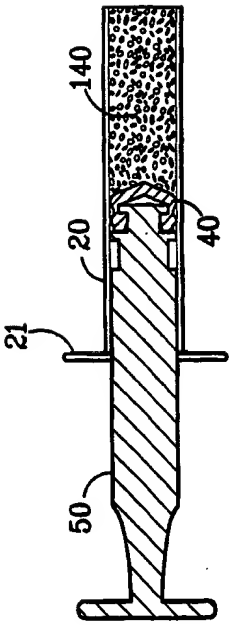

FIG. 6B

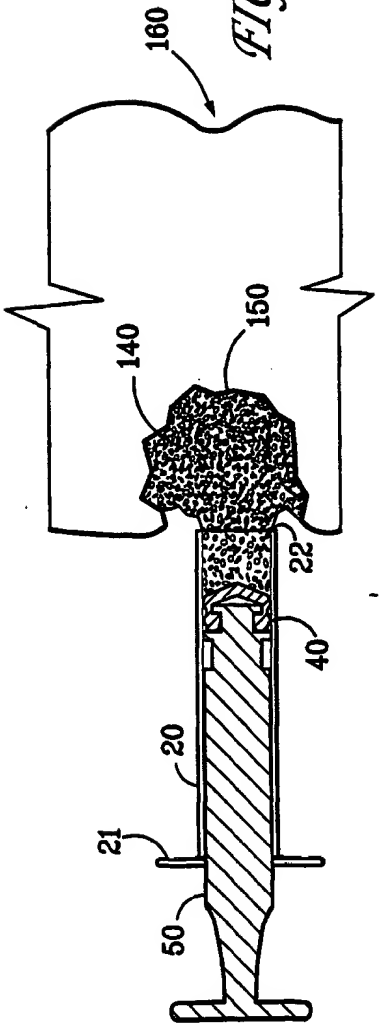

FIG. 6C